EXHIBIT A47

Douching, Talc Use, and Risk of Ovarian Cancer

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Background: Douching was recently reported to be associated with elevated levels of urinary metabolites of endocrine disrupting phthalates, but there is no literature on douching in relation to ovarian cancer. Numerous case–control studies of genital talc use have reported an increased risk of ovarian cancer, but prospective cohort studies have not uniformly confirmed this association. Behavioral correlation between talc use and douching could produce confounding.

Methods: The Sister Study (2003–2009) enrolled and followed 50,884 women in the US and Puerto Rico who had a sister diagnosed with breast cancer. At baseline, participants were asked about douching and talc use during the previous 12 months. During follow-up (median of 6.6 years), 154 participants reported a diagnosis of ovarian cancer. We computed adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for ovarian cancer risk using the Cox proportional hazards model.

Results: There was little association between baseline perineal talc use and subsequent ovarian cancer (HR: 0.73, CI: 0.44, 1.2). Douching was more common among talc users (odds ratio: 2.1, CI: 2.0, 2.3), and douching at baseline was associated with increased subsequent risk of ovarian cancer (HR: 1.8, CI: 1.2, 2.8).

Conclusions: Douching but not talc use was associated with increased risk of ovarian cancer in the Sister Study.

(*Epidemiology* 2016;27: 797–802)

Cancer of the ovary is the most lethal gynecological cancer in women, and its etiologies remain poorly understood. In 2015, there were an estimated 21,290 new cases and 14,180 ovarian cancer deaths among women in the United States.[1] Family history of ovarian or breast cancer is a major risk factor. Nulliparity is also associated with increased risk of ovarian cancer, whereas tubal ligation and oral contraceptive use are reportedly associated with reduced risk.[2]

Genital talc use and douching could plausibly introduce particles and toxicants into the upper reproductive tract and increase the risk of cancers and infections. Talc particles have been found embedded in cervical and ovarian tumors.[3] Fragranced douching products can contain phthalates, which disrupt endocrine pathways and could influence ovarian cancer risk through hormone disruption.[4] A recent analysis of data from the National Health and Nutrition Examination Survey found an association between douching and urinary concentrations of phthalates.[5] Douching has also been associated with adverse health effects and reproductive problems, such as pelvic inflammatory disease and ectopic pregnancy,[6] as well as decreased fertility.[7]

To the best of our knowledge, no existing studies have investigated the association between douching and ovarian cancer, but talc use was associated with ovarian cancer in many case–control studies.[8–13] A meta-analysis of 14 population-based, case–control studies[14] and a large, pooled case–control analysis[15] both reported positive associations between genital talc use (ever vs. never) and ovarian cancer. The only prospective studies to examine talc and ovarian cancer[16,17] found no strong associations overall, but one observed increased risk for invasive serous ovarian cancer, specifically.[17] In this study, we investigate the association between ovarian cancer and both douching and talc use, using prospective data from the Sister Study cohort.

METHODS

The Sister Study, launched in 2003, enrolled 50,884 women across the United States and Puerto Rico. Enrollees were aged 35 to 74 years and had never had breast cancer but each had a full or half-sister who had been diagnosed with breast cancer. More than one sister per family could participate.

After excluding participants who had bilateral oophorectomies (N = 9,023) or ovarian cancer (N = 167) before enrollment or who had no follow-up information (N = 40), we included 41,654 participants in this analysis. As of July 2014 (median follow-up 6.5 years), 154 incident ovarian cancer cases had occurred. We included tumors of the ovary (N = 135), fallopian tubes (N = 7), peritoneum (N = 4), or of uncertain origin but likely from one of the three aforementioned

Submitted 18 April 2016; accepted 15 June 2016.

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Supported by the Intramural Research Program of the National Institutes of Health, National Institute of Environmental Health Sciences (Project Z01-ES044005 to DPS).

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The authors report no conflicts of interest.

SDC Supplemental digital content is available through direct URL citations in the HTML and PDF versions of this article (www.epidem.com).

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ISSN: 1044-3983/16/2706-0797
DOI: 10.1097/EDE.0000000000000528

primary sites (N = 8). The Institutional Review Boards of the National Institute of Environmental Health Sciences and the Copernicus Group approved this study and all participants provided written consent.

Participants completed computer-assisted telephone interviews, which included questions about reproductive history (including any oophorectomies), health conditions, and lifestyle factors. Participants also completed a self-administered questionnaire about personal care products used in the 12 months before enrollment, which included questions about frequency of douching and about genital talc use in the form of powder or spray applied to a sanitary napkin, underwear, diaphragm, cervical cap, or vaginal area. Response categories were: did not use, used less than once a month, used 1–3 times per month, 1–5 times per week, or more than 5 times per week. Because most members of the cohort reported not douching and not using talc, we used dichotomous use/nonuse variables for analysis.

Updated information on oophorectomies was collected in follow-up questionnaires administered every 2–3 years. We ascertained information on any new cancers via an annual health update and the follow-up questionnaires and were able to confirm 96 of the ovarian cancer cases using medical records (N = 87) or death certificate/National Death Index data (N = 9). For the remaining 58 cases, we relied on information provided by the participant herself (N = 52) or her next of kin (N = 6). Among women with available medical records who self-reported ovarian cancer, 90% were confirmed.

There were five eligible cases with an unknown exact age at diagnosis. For them, we imputed an age midway between their last ovarian cancer-free follow-up interview and their age at the time we were notified of the diagnosis (or death). Although we did not genotype women directly for *BRCA1* or *BRCA2* mutations, we asked each woman in her baseline interview whether she had ever been tested and, if so, what the result of those tests were. For the purposes of this analysis, a woman was treated as *BRCA1/2* mutation positive if (1) she had a positive test or (2) she had a sister with a known positive test and she had no known negative test.

Statistical Analyses

We computed adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the association of talc use and douching with ovarian cancer risk using Cox proportional hazards models, with age as the primary time scale. Follow-up lasted from age at baseline until age at diagnosis of ovarian cancer. Follow-up time was censored at their age of bilateral oophorectomy after baseline, death, or last contact. Because some participants had sisters who also enrolled in the cohort, we used generalized estimating equation methods to calculate robust variances to account for family clustering. We evaluated proportionality assumptions of the Cox model by assessing the improvement in goodness-of-fit provided by including an age-by-factor interaction term.

In addition to the main effect, we evaluated the joint effect of both douching and using talc. We classified participants into four categories: neither exposure, talc use exclusively, douching exclusively, or both exposures. We also carried out a number of stratified analyses. We stratified by reproductive factors, such as menopausal status, parity, hysterectomy, and tubal ligation to explore possible effect modification.[10,13] We tested for differences across strata using the *P* value for an exposure-by-modifier interaction term.

We selected potential confounders or effect modifiers of the association between ovarian cancer and the exposures of interest in this analysis a priori based on assumed causal relationships among the covariates,[18] and included patency (yes/no blockage of reproductive tract by tubal ligation or hysterectomy), menopausal status (pre- or postmenopausal), duration of oral contraceptive use (none, <2 years, 2-<10 years, 10 or more years), parity (yes/no), race (non-Hispanic white, non-Hispanic black, Hispanic or other), and body mass index (<25, 25–29.9, or >30 kg/m^2), all of which were fixed at baseline levels.

We conducted six sensitivity analyses. In the first, we restricted to the 96 cases confirmed by medical record or death certificate/National Death Index data. For our second sensitivity analysis, we looked for evidence of etiologic heterogeneity by further restricting this pool to medically confirmed cases with serous ovarian cancer (N = 49). For our third sensitivity analysis, we included all 154 eligible ovarian cancer cases as well as five additional cases that had unknown ages at diagnosis and prebaseline oophorectomies (N = 159 cases total). We did this to examine the influence of our assumptions about the relative timing of their oophorectomies versus their ovarian cancer diagnoses. We further examined the influence of imputing age at diagnosis in our fourth sensitivity analysis by excluding the five cases with imputed diagnosis ages but intact ovaries (N = 149 cases total). For our fifth sensitivity analysis, we excluded participants from families known to carry *BRCA* mutations (N = 347 exclusions, including 10 cases) since the lifetime risk of ovarian cancer for individuals with a *BRCA1/2* mutation is substantially higher[19] and the etiology may be different. Finally, we conducted analyses excluding the first year of follow-up, to minimize the possibility that symptoms of undiagnosed ovarian cancer were leading participants to use douche or talc. All analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC) and using the Sister Study data release version 4.1.

RESULTS

Table 1 summarizes characteristics of cases and noncases at baseline. Most participants were non-Hispanic white (84%), and most were postmenopausal (56%). Women who later became cases were somewhat older (mean 57.8 vs. 54.8), more often white, and more often nulliparous. Cases were also more likely to have a first-degree family history of ovarian cancer and more than one first-degree relative with

TABLE 1. Baseline Characteristics of the Sister Study Cohort (2003–2009)[a]

	Noncases (N = 41,500)	Ovarian Cancer Cases (N = 154)
Race; N (%)		
Non-Hispanic White	34,745 (84)	138 (90)
Non-Hispanic Black	3,598 (9)	9 (6)
Hispanic	2,076 (5)	5 (3)
Other	1,068 (2)	2 (1)
Education; N (%)		
High school or less	6,001 (14)	24 (15)
Some college	13,556 (33)	49 (32)
Bachelor's degree	11,579 (28)	46 (30)
Graduate degree	10,354 (25)	35 (23)
BMI; N (%)		
<25.0 kg/m^2	16,610 (40)	51 (33)
25–29.9 kg/m^2	13,012 (31)	51 (33)
≥30 kg/m^2	11,866 (29)	52 (34)
Menopausal status; N (%)		
Premenopausal	15,238 (37)	40 (26)
Hysterectomy with ovaries retained	2,996 (7)	8 (5)
Postmenopausal	23,239 (56)	106 (69)
Hysterectomy; N (%)		
No	34,481 (83)	120 (78)
Yes	6,995 (17)	34 (22)
Tubal ligation; N (%)		
No	29,511 (71)	115 (75)
Yes	11,973 (29)	39 (25)
Oral contraception		
Duration of Use; N (%)		
None	6,452 (16)	25 (16)
<2 years	6,382 (15)	37 (24)
2–10 years	17,769 (43)	67 (44)
10 years or more	10,865 (26)	25 (16)
Parity; N (%)		
No live births	7,657 (18)	37 (24)
1 or more live births	33,816 (82)	116 (76)
First-degree family history of ovarian cancer; N (%)		
No	40,149 (97)	138 (90)
≥1 first-degree relative	1,322 (3)	16 (10)
Breast cancer; N (%)		
1 affected sister	31,291 (75)	109 (71)
>1 sister or sister + mom	10,207 (25)	45 (29)
BRCA1/2 mutation status; N (%)		
No known mutation	41,163 (99)	144 (94)
Known mutation	337 (1)	10 (6)

Missing values: race (13 noncases), education (10 noncases), BMI (12 noncases), menopausal status (27 noncases), tubal ligation (16 noncases), hysterectomy (24 noncases), oral contraception use (32 noncases), parity (1 case, 27 noncases), ovarian cancer family history (29 noncases), and breast cancer family history (2 noncases).

[a]Excludes women who were diagnosed with ovarian cancer before completion of the baseline interview (N = 167), women who had a bilateral oophorectomy before the baseline interview (N = 9,023), and women lost to follow-up (N = 40).

BMI indicates body mass index.

breast cancer. They were also more likely to carry a deleterious mutation in *BRCA1* or *BRCA2*. While ever/never use of oral contraceptive was similar across cases and noncases, the distribution of duration of use differed. More noncases (26%) than cases (16%) had used oral contraceptives for more than 10 years. Compared with women who neither douched nor used talc, women who douched were more likely to be non-Hispanic black (23% vs. 6%) and to have less than a college degree (62% vs. 44%) and women who used talc were more likely to have a body mass index over 30 kg/m^2 (41% vs. 25%; eTable; http://links.lww.com/EDE/B74).

Douching in the 12 months before study enrollment was reported by 13% of noncases and 20% of cases (Table 2). Talc use in the 12 months before study enrollment was reported by 14% of noncases and 12% of cases. Only seven cases (5%) reported both douching and talc use.

Ever douching during the 12 months before study entry was associated with increased ovarian cancer risk (adjusted HR: 1.8, 95% CI: 1.2, 2.8; Table 2). By contrast, talc use during the 12 months before study entry was associated with reduced risk after the same confounder adjustments (HR: 0.73, CI: 0.44, 1.2) and there was a negligible change in the estimated effect with additional adjustment for douching (HR: 0.70, CI: 0.42, 1.1). We observed no proportional hazards assumption violations for any of the examined models.

Douching with no talc use was also associated with increased risk of ovarian cancer compared with use of neither talc nor douching (adjusted HR: 1.9, CI: 1.2, 2.9), which is similar to the overall effect estimate of douching. There was an inverse association between exclusive talc use and ovarian cancer, and a positive association for douching and talc use combined (HR: 1.8, CI: 0.81, 3.9). There was no evidence for interaction on a multiplicative ($P = 0.39$) or additive ($P = 0.72$) scale.

To explore effect modification, we performed analyses stratified by a number of reproductive factors including tubal ligation status, hysterectomy status, menopause status, and parity (Figure). We also stratified by patency to see if blockage of access to the ovaries by either tubal ligation or hysterectomy might modify the association between ovarian cancer and douching or talc use. For all stratifications, there were no modifications of effect estimates for either douching or talc use (all heterogeneity P values >0.05).

HRs for talc use differed little in the first five sensitivity analyses, showing a HR change no greater than 0.04. By contrast, exclusion of ovarian cancers without medical record or death certificate confirmation (by censoring their follow-up at the reported diagnosis age) attenuated the association between douching and ovarian cancer (HR: 1.1, CI: 0.62, 2.1). Likewise, restriction to medically confirmed serous ovarian cancer also attenuated effect estimates (HR: 1.4, CI: 0.64, 3.2). However, ovarian cancer cases who had reported that they douched were substantially less likely to have a medical record available (40%) than ovarian cases who did not douche (69%),

suggesting that medical records were informatively missing, biasing results based on the restricted analysis. There was very little change in douching effect estimates when excluding the five cases with uncertain diagnosis dates or including the five women reporting oophorectomies before the diagnosis of ovarian cancer. Exclusion of known positive *BRCA1/2* families slightly strengthened the association between douching and ovarian cancer (HR: 1.9, CI: 1.3, 2.9). In our sixth sensitivity analysis, exclusion of the first year of follow-up time resulted in negligible changes in the HRs for douching and talc use (HR: 1.8, CI: 1.2, 2.8 and HR: 0.86, CI: 0.52, 1.4, respectively).

DISCUSSION

In this large prospective cohort, which gave rise to 154 incident cases of ovarian cancer, there was a positive association between douching and incident ovarian cancer. Talc use was associated with a slight reduction of ovarian cancer risk. Our study of ovarian cancer grouped together all cancers designated as ovarian (88%), fallopian (5%), peritoneal (3%), or those designated as uncertain but ovarian, fallopian, or peritoneal (5%). With recent literature suggesting that most cancers classified as ovarian likely originated in the fallopian tubes,[20] we felt that this grouping was appropriate.

Interest in talc as a carcinogen arose because of its chemical similarity to asbestos, which has been previously linked to ovarian cancer.[21] One challenge with studying talc is that the chemical formulation of talc has changed over time,[9] and not all powders contain the mineral talc (e.g., cornstarch-based products). Previous case–control studies have noted evidence for a positive association,[8–13] with some evidence that the effect is strongest in premenopausal women.[13] Given these results, the biological plausibility, the rarity of the exposure, and imprecision of estimates, we cannot exclude a small increase in risk associated with talc use, despite our inverse findings. Then again, with the exception of the finding that talc use was positively associated with serous ovarian cancer in the Nurses' Health Study,[17] the prospective studies have not provided evidence supporting an association between talc use and ovarian cancer overall[17] or between talc use and ovarian cancer overall among postmenopausal women.[16]

The numbers for the Sister Study as a whole given in Table 2 reveal an odds ratio of 2.1 (CI: 2.0, 2.3) for douching in relation to talc use. Thus, the two practices are correlated. If douching is a risk factor for ovarian cancer, some of the earlier reports on talc could have been subject to confounding bias. However, the one case–control study that did include douching as a covariate still observed a positive association between talc use and ovarian cancer risk.[8] Another factor that may contribute to our null findings is that we categorized the exposure based on the 12 months before enrollment as a dichotomous ever/never factor rather than a quantitative measure of total applications, as has been done in previous studies.

Because Sister Study participants all have a first-degree family history of breast cancer, they are more likely than the general population to develop ovarian cancer (estimated observed/expected number of cases = 1.6 based on SEER rates). We also note that, by design, we excluded women with a previous history of breast cancer, thereby discounting some individuals who were at increased risk for ovarian cancer. While these selective factors may limit generalizability, there is no clear mechanism by which they would bias the estimated effect of talc use or douching on ovarian cancer.

Our review of the literature suggests that our study is the first to examine the association between douching and ovarian cancer. This association could reflect uncontrolled confounding by behavioral factors we have not captured well. For example, women may be more likely to douche if they are prone to infections or other reproductive health problems that could themselves be related to ovarian cancer.

If the association is causal, it could be related to the recently reported positive association between douching

TABLE 2. Exposure Prevalence and Hazard Ratios for Their Associations with Ovarian Cancer in the Sister Study

	Noncases (N = 41,500)	Ovarian Cases (N = 154)	Fully Adjusted Hazard Ratio[a]
Douching past 12 months			
No	34,653 (87)	121 (80)	1.00
Yes	5,364 (13)	30 (20)	1.8 (1.2, 2.8)
Talc use past 12 months			
No	33,770 (86)	130 (88)	1.00
Yes	5,718 (14)	17 (12)	0.73 (0.44, 1.2)
Douched and used talcum powder past 12 months			
Neither	29,596 (76)	106 (72)	1.00
Talc use/no douching	4,399 (11)	10 (7)	0.60 (0.31, 1.1)
Douching/no talc use	3,936 (10)	23 (16)	1.9 (1.2, 2.9)
Both	1,237 (3)	7 (5)	1.8 (0.81, 3.9)

Missing values: douching (3 cases, 1,483 noncases), talc use (7 cases, 2,012 noncases).
[a]Adjusted for race, body mass index, parity, duration of oral contraceptive use, baseline menopause status, and patency.

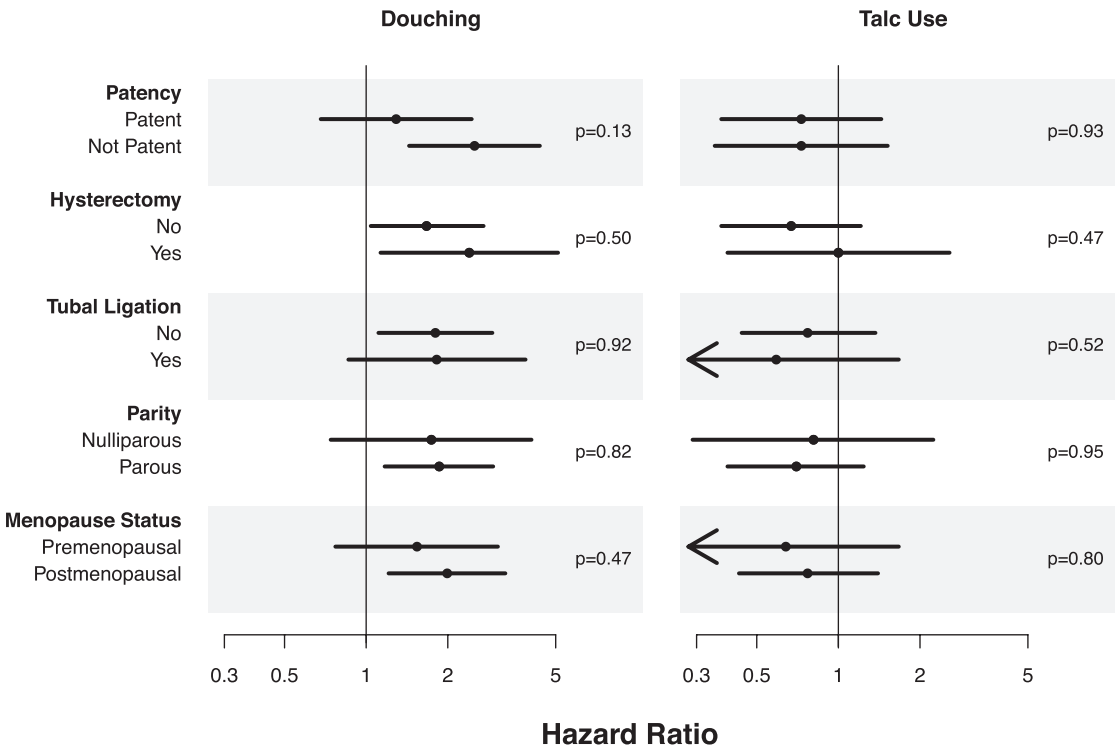

FIGURE. Effect estimates of douching and talc use in the Sister Study when stratified by multiple reproductive factor, adjusted for race, body mass index, parity, duration of oral contraceptive use, baseline menopause status, and patency. The reported heterogeneity *P* values are for tests of an exposure-by-modifier interaction term.

and higher urinary levels of phthalate metabolites observed in National Health and Nutrition Examination Survey participants.[5] Phthalates are endocrine-disrupting chemicals and may be harmful to the fallopian tubes or the ovaries.[22] In an animal study, exposure to di-(2-ethylhexyl) phthalate at 500 and 2,000 mg/kg demonstrated ovarian toxicity through decreased progesterone and increased apoptosis in granulosa cells.[23] Furthermore, ovarian cancer cell lines have been found to increase cell proliferation and to up-regulate cell-cycle regulatory genes following treatment with di-*n*-butyl phthalate.[24] We did not collect detailed information about specific products used in douching, so we are unable to estimate exposure to individual phthalates.

Douching could also force tissue, menstrual fluids, or foreign materials up the reproductive tract, resulting in inflammation (e.g., pelvic inflammatory disease[6]) or infection of the fallopian tubes or ovaries themselves. This inflammation and infection could also contribute to ovarian cancer risk, as supported by the observed positive association between pelvic inflammatory disease and ovarian cancer.[25]

If the association is causal and related to the transfer of xenobiotics into the upper reproductive tract, we would expect to see a stronger association in women with both a uterus and patent fallopian tubes. However, the evidence in our data appeared to be driven by the subcohort of women with hysterectomy and/or tubal ligation (Figure).

Because our study was prospective in nature, it is robust to potential differential reporting bias as exposures are recorded before development of cancer. Another important strength of the study was that we controlled for many potentially confounding factors.

An important limitation of our study is that we collected douching and talc information on individuals for the year before study entry and have not accounted for the latency of ovarian cancer, which is likely to be long.[26] If latency is 15 to 20 years, douching habits at baseline do not accurately reflect the period of risk, although women who douched at baseline are likely to have been douching for a substantial amount of time before that as well. Also, given that there have been health advisories against douching because of its other potential risks, participants who douched in the past may have stopped douching and would be misclassified. Thus, the relative risk for douching in relation to ovarian cancer could be underestimated. Future studies that ascertain a complete history of douching are warranted.

Although the baseline questionnaire did ask women about their use of douche and talc between the ages 10 and 13, very few women responded yes to douching (2%), and we were unable to make use of those data. By contrast, talc use during ages 10–13 had a prevalence of 18% in the cohort, but there was no detectable effect of prepubertal talc use on risk (HR: 1.1, CI: 0.74, 1.7).

Exposure information was very complete, with only 831 participants (2%) missing the personal care products questionnaire entirely, and an additional 655 and 1,188 missing data for the questions about douching or talc use, respectively. However, for approximately 37% of cases, we have not yet received medical records to confirm the diagnosis. We found that medical record retrieval was differential by exposure, with a lower proportion with medical records among women who douched than among women who did not. This informative missingness mathematically contributed to the substantial attenuation in the HR estimate for the association between vaginal douching and ovarian cancer when we restricted to cases with medical record confirmation. Medical record retrieval for ovarian cancer began only recently, and women with cancers diagnosed early in follow-up are more likely to be missing medical record information. Some of the unconfirmed diagnoses may be confirmed later via medical records or the national death index.

In this large, prospective study, we did not observe an association between recent talc use and ovarian cancer risk, but did find a strong positive association between douching and ovarian cancer risk.

ACKNOWLEDGMENTS

The authors thank Drs. Kristen Upson and Annah Wyss for comments on an early draft of this article.

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